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Clinical Equivalence of Controlled-Release Oxycodone 20 mg and Controlled-Release Tramadol 200 mg after Surgery for Breast Cancer

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Key Words
Analgesic efficacy · Breast surgery · Oxycodone · Postoperative analgesia · Tramadol

Abstract
Aims: To assess clinical equivalence of 20 mg controlled-release oxycodone (Oxygesic®; Mundipharma, Limburg, Germany) and 200 mg controlled-release tramadol (Tramal long®; Grünenthal, Aachen, Germany) on a 12-hour dosing schedule in a randomized, double-blinded study of 54 ASA I–III physical status (American Society of Anesthesiologists classification of physical status) patients undergoing surgery for breast cancer. ***Methods:*** General anesthesia using remifentanil and propofol was performed for surgery. Patients were randomly allocated to 2 groups, receiving either 20 mg controlled-release oxycodone (Oxy group) or 200 mg controlled-release tramadol (Trama group) with the premedication (7.5 mg midazolam) and again 12 hours later. All patients had access to rescue medication (i.v. paracetamol). The primary variables for clinical equivalence were the differences between the mean values for pain scores at rest and pain scores on coughing over 24 hours after operation. The equivalence margin was determined as ±10 on the visual analogue scale. ***Results:*** Fifty-four patients were enrolled. Regarding pain scores at rest, the 90% CI of the mean differences between the treatment groups over 24 hours after operation was found to be within the predefined equivalence margin [–4.5 to +1.7], and the CI values for pain scores on coughing [–6.2 to +1.7] were similar. Cumulative paracetamol given over the 24-hour observation period did not differ significantly between the Oxy group (1.32 ±1.9 g) and the Trama group (1.61 ± 1.1 g; p = 0.32). There were no significant differences between the treatment groups regarding adverse events such as nausea (p = 0.13), vomiting (p = 0.24) and itching (p = 0.77). Also, no differences were found concerning patient satisfaction scores (p = 0.8) or patients' general perception of postoperative pain management (p = 0.71). ***Conclusion:*** 20 mg controlled-release oxycodone is clinically equivalent to 200 mg controlled-release tramadol for postoperative analgesia after surgery for breast cancer.

Introduction

The treatment of chronic pain has been optimized by the use of controlled-release formulas, and a basic oral medication is effective with 1 or 2 doses a day. A similar approach to postoperative pain management can have

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economic advantages, because it results in time savings for health care personnel and patients may be discharged from the hospital earlier. Remifentanil-based anesthesia with rapid recovery motivated us to compare 2 oral controlled-release pain treatments in the management of postoperative pain after surgery for breast cancer.

Oxycodone, derived from thebaine, was introduced into clinical practice in Germany in 1917 [1] and became an established drug for the treatment of chronic cancer pain [2–4]. Predictable pharmacokinetics, rapid onset of action, no ceiling dose, and minimal adverse effects contributed to its successful use in the treatment of postoperative pain [5–8]. A low incidence of nausea and vomiting compared to other opioids was found in some studies [9, 10], with controlled-release oxycodone causing fewer adverse events than immediate-release oxycodone [3, 7, 11].

Tramadol is a centrally acting, synthetic analgesic with a dual mechanism of action that involves a weak affinity for opioid μ-receptors as well as the inhibition of reuptake of serotonin and norepinephrine [12, 13]. The complementary and synergistic actions of its 2 enantiomers enhance its analgesic effect and improve its tolerability profile [14]. In contrast to pure opioid agonists, it has a low risk of respiratory depression, tolerance and dependence [15]. It is not classified as a controlled drug and has been in use in Germany since 1977. Tramadol has proved to be an effective and well-tolerated analgesic in the treatment of acute and chronic pain [14, 16], the most common side effects being nausea and vomiting [17–19].

The purpose of the present study was to assess clinical equivalence of controlled-release oxycodone 20 mg and controlled-release tramadol 200 mg administered in a 24-hour dosing schedule for postoperative analgesia in patients after surgery for breast cancer.

Materials and Methods

After obtaining local research committee approval (ethics committee of the Medical Faculty, University of Cologne), patients were enrolled in our randomized, double-blinded study, which was conducted in accordance with the Declaration of Helsinki. Eligible patients were those scheduled for surgery for breast cancer, who were aged 18–80 years, had ASA physical status I–III and weighed 40–100 kg. Patients with known contraindications for oxycodone, tramadol and paracetamol were excluded. Further exclusion criteria were communication difficulties, psychiatric diseases, pregnancy, a history of alcoholism or drug abuse, chronic pain or sleep apnea syndrome.

Randomization was based on a computer-generated code prepared at a remote site and sealed in sequentially numbered, opaque envelopes. The patients were randomly allocated to 2 groups, the controlled-release oxycodone (Oxygesic®; Mundipharma, Limburg, Germany) group (Oxy group) or the controlled-release tramadol (Tramal long®; Grünenthal, Aachen, Germany) group (Trama group).

Thirty minutes before surgery, premedication with oral midazolam 7.5 mg was given to all patients. The Oxy group and the Trama group received 1 tablet of 20 mg controlled-release oxycodone or 1 tablet of 200 mg controlled-release tramadol, respectively, at the time of the premedication and 12 h later. Patients and investigators were blinded to the identity of the study treatment by double dummy. In the operating room, routine monitoring of non-invasive arterial blood pressure, electrocardiogram, and pulse oxymetry was initiated. Remifentanil was started at 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Patients were preoxygenated with 100% oxygen. After 3 min, propofol 1–2 $mg \cdot kg^{-1}$ was injected. Tracheal intubation was facilitated with mivacurium 0.2 $mg \cdot kg^{-1}$, and patients' lungs were ventilated mechanically with an oxygen/air mixture to maintain end-tidal CO_2 at 4–4.7 kPa. Maintenance of anesthesia was performed by remifentanil and propofol at the discretion of the anesthesiologist. After extubating the trachea, patients were transferred to the recovery room. All patients had access to rescue medication, if necessary (1 g of i.v. paracetamol; Perfalgan®; Bristol-Myers Squibb, Munich, Germany). Discharge of patients from the recovery area was at the discretion of the attending anesthesiologist.

All postoperative assessments at 8, 16 and 24 h after the premedication time were performed by one of the authors blinded to group assignment (S.S.). Monitoring at each assessment point included noninvasive blood pressure as well as heart and respiratory rate. Wound pain at rest and on coughing was assessed using a 100-mm visual analogue scale (VAS), which ranged from 0 (no pain) to 100 (worst pain imaginable).

Hypotension was defined as systolic blood pressure <80 mm Hg or >30% decrease compared with baseline, and hypertension was defined as blood pressure >180 mm Hg systolic or 110 mm Hg diastolic. Bradycardia was defined as heart rate <50 bpm, and tachycardia was defined as heart rate >120 bpm. Bradypnea was defined as a respiratory rate <12 $breaths \cdot min^{-1}$, and tachypnea was defined as a respiratory rate >20 $breaths \cdot min^{-1}$. Sedation was recorded on a 4-point scale (0 = no signs of sedation, 1 = mild sedation, 2 = moderate sedation, 3 = severe sedation). The incidence of pruritus, nausea and vomiting was recorded after direct questioning of the patients. The quality of patient satisfaction (4-point scale: 1 = poor, 2 = fair, 3 = good, 4 = excellent) was assessed at each observation point. In addition, the patients were asked to give a general evaluation of their pain treatment at the last observation point (4-point scale: 4 = poor, 3 = fair, 2 = good, 1 = excellent).

Statistics

Statistical analysis was performed with ANOVA for repeated measurements and t tests for independent samples by using the SPSS 13.0 statistical package (SPSS Inc., Chicago, Ill., USA) as well as Fisher's exact test using Stata 8. Sample size determination was performed using Pass (Number Cruncher Statistical Systems Inc., Kaysville, Utah, USA).

We tested the hypothesis that controlled-release oxycodone (Oxygesic) 20 mg is clinically equivalent to controlled-release tramadol (Tramal long). The primary variables for clinical equiva-

Table 1. Demographics (data are means ± SD or numbers)

	Oxy group (n = 26)	Trama group (n = 27)
Age, years	56.3 ± 8.6	54.9 ± 9.5
Weight, kg	67.6 ± 10.9	71.9 ± 14.8
Body Mass Index	24.6 ± 3.44	25.2 ± 4.83
ASA physical status I/II/III, n	4/21/1	8/18/1

Table 2. Surgical procedures

	Oxy group (n = 26)	Trama group (n = 27)
Breast-conserving therapy, axillary lymph node dissection	16 (80%)	17 (85%)
Total mastectomy, axillary lymph node dissection	4 (20%)	3 (15%)

Table 3. Duration of surgical procedures (in min)

	Oxy group (n = 26)	Trama group (n = 27)	p	95% CI
Duration of surgery	76.35 ± 30.32	86.48 ± 28.07	0.21	–6 to 26.27

Table 4. VAS pain scores at rest (VAS runs from 0 to 100 mm)

Treatment group		Mean	SD
After 8 h	Oxycodone	12.7	13.13
	Tramadol	15.6	12.51
After 16 h	Oxycodone	8.5	8.34
	Tramadol	7.8	5.77
After 24 h	Oxycodone	5.4	5.82
	Tramadol	7.4	8.59

Oxy group: n = 26; Trama group: n = 27.

Table 5. VAS pain scores on coughing (VAS runs from 0 to 100 mm)

Treatment group		Mean	SD
After 8 h	Oxycodone	13.8	13.59
	Tramadol	15.6	12.51
After 16 h	Oxycodone	8.5	8.34
	Tramadol	8.1	6.81
After 24 h	Oxycodone	6.2	5.71
	Tramadol	11.5	21.43

Oxy group: n = 26; Trama group: n = 27.

lence were the differences between the mean values for the pain scores at rest and on coughing (8–24 h). The result of the sample size determination for an equivalence test of means using two 1-sided tests on data from a parallel-group design was a sample size of 27 in both the reference and treatment groups, with a 95% power at a 1-sided 5% significance level – thus an overall significance level of 10% – when the true difference between the means is zero, the standard deviation is 10, and the equivalence margin is ±10 (units: mm VAS).

Evaluation of the intrasubject variability of the VAS in the postoperative period resulted in detecting an imprecision of ±20 mm [20]. Thus, we chose ±10 mm on the VAS as equivalence margin, which was less than the expected amount of imprecision for a single VAS score.

The quality of analgesia at each time of assessment was analyzed using a 2-tailed t test. Adverse events, such as itching or postoperative nausea and vomiting, were analyzed using Fisher's exact test. The study groups were compared by 2-tailed t tests with regard to cumulative consumption of rescue medication and patient satisfaction. Demographic data are presented descriptively. Significance was determined at a p value of <0.05. Unless indicated, data are presented as means ± SD.

Results

In 2005, 54 female patients were enrolled in our study, 27 in the Oxy group and 27 in the Trama group. The data of 53 patients were eligible for statistical analysis. Due to postoperative complications requiring operative revision, the data of 1 patient in the Oxy group had to be excluded from analysis. All other patients received the medication as stated in the study protocol.

The Oxy group and the Trama group were comparable regarding age (56.3 ± 8.6; 54 ± 9.5; p = 0.34), weight (67.6 ± 10.9; 71.9 ± 14.8; p = 0.23), and Body Mass Index (24.6 ± 3.44; 25.2 ± 4.83; p = 0.58; table 1). Surgical procedures did not differ between the groups (tables 2 and 3).

The mean values of the pain scores at rest and on coughing are presented in tables 4 and 5, respectively. Since 90% CIs are more suitable for equivalence studies than 95% CIs [21–23] we provided these. The 90% CI of the mean differences between the treatment groups during the postoperative observation time (8–24 h) in VAS at

Table 6. Adverse effects: nausea

Nausea	Oxy group (n = 26)	Trama group (n = 27)	p	95% CI
After 8 h	7 (26.9%)	4 (14.8%)	0.29	–0.13 to 0.37
After 16 h	8 (30.8%)	4 (14.8%)	0.17	–0.1 to 0.42
After 24 h	6 (23.%)	5 (18.5%)	0.69	–0.2 to 0.29

Table 7. Adverse effects: vomiting

Vomiting	Oxy group (n = 26)	Trama group (n = 27)	p	95% CI
After 8 h	5 (19.2%)	1 (3.7%)	0.08	–0.28 to 0.34
After 16 h	5 (19.2%)	5 (18.5%)	0.95	–0.23 to 0.24
After 24 h	3 (11.5%)	2 (7.4%)	0.62	–0.12 to 0.21

rest was [–4.5 to +1.7]. This interval was found to be within the predefined interval of [–10.0 to +10.0]. It was therefore concluded that the 2 treatments were clinically equivalent.

The 90% CI of the mean differences over the postoperative observation time (8–24 h) between the treatment groups in VAS on coughing [–6.2 to +1.7] was found to be within the defined margin for the primary objective VAS at rest [–10.0 to +10.0], supporting the primary hypothesis of clinical equivalence.

The cumulative amount of i.v. paracetamol given during the first 24 h after operation did not differ significantly between the Oxy group (1.31 ± 1.9 g) and the Trama group (1.61 ± 1.1 g; p = 0.32). The patient satisfaction scores revealed excellent ratings at each time of assessment (Oxy group 3.56 ± 0.09; Trama group 3.53 ± 0.09; p = 0.8). Also, the results for the general assessment of postoperative pain management (Oxy group 1.54 ± 0.58; Trama group 1.48 ± 0.51; p = 0.71) were equally good in both treatment groups.

No significant difference between treatment groups could be detected with regard to adverse events. The figures for nausea (p = 0.13) and vomiting (p = 0.24) are shown in tables 6 and 7, giving the number of patients with adverse effects. There were no differences in itching (p = 0.77), sedation (p = 0.97) and dizziness (p = 0.35) between the Oxy and the Trama groups.

Discussion

In a previous placebo-controlled study we proved the effectiveness of controlled-release oxycodone 20 mg in preventing postoperative pain after breast surgery for cancer [24]. Another study showed that controlled-release oxycodone was better tolerated than i.v. tramadol/metamizol for postoperative analgesia after retinal surgery, resulting in a better quality of analgesia and less nausea [10]. This motivated us to compare the effectiveness of oxycodone and tramadol as controlled-release oral medication for postoperative pain after breast surgery for cancer in an equivalence trial.

The dosing scheme of 20 mg controlled-release oxycodone and 200 mg controlled-release tramadol resulted from considering morphine equivalences and the existing dosing scheme in our clinic. Due to the interindividual variations in the bioavailability of oral oxycodone and morphine, the determination of the relative potency between these 2 substances is problematic [25]. Several reports suggest that oral oxycodone may range from equipotent to twice as potent [26]. i.v. tramadol compared to i.v. morphine showed equipotent dose ratios between 6.3:1 and 10.2:1 [27].

Because of the higher oral bioavailability of tramadol, the equivalent oral tramadol dose is expected to be even lower [14]. When choosing oxycodone or tramadol for postoperative pain management, the standard procedure in our clinic is currently either 20 mg oxycodone SR or 200 mg tramadol SR, thus assuming an equipotent dose ratio of 1:10.

Based on the assumption that 2 clinically equivalent treatments should not differ by more than a specific amount [21, 28], we chose ±10 mm on the VAS as equivalence margin. Due to its good correlation with acute pain levels, the VAS is a valid and reliable instrument for the assessment of postoperative pain [29, 30]. Because of the linear scale properties of the VAS, a relative change of pain intensity is expressed by a change in the VAS score [31, 32]. A series of paired measurements in acute pain found 95% of the pain ratings to be within 16 mm on the VAS [33]. A variability of up to 20% was detected in experimental serial VAS measurements [34]. Evaluating the intrasubject variability of the VAS in the postoperative period resulted in detecting an imprecision of ±20 mm. Any single VAS score may not be a true measure of pain but should be considered as accurate as ±20 mm [20]. Our predefined equivalence margin of ±10 mm on the VAS is less than the expected amount of imprecision for

a single VAS score. The CIs found in this study lie entirely within the predefined equivalence margin, indicating clinical equivalence regarding pain scores at rest and on coughing. The fact that similar amounts of rescue medication were needed supports these findings. Sample size determination and adherence to the study protocol contributed to the outcome of this study. Only 1 patient, in the Oxy group, had to be excluded from the study protocol because of postoperative bleeding and the need for operative revision.

Evaluation of the incidence of adverse events revealed no significant differences between the 2 groups. Unlike in our previous study, the patients in the Trama group did not experience significantly more nausea or vomiting [10]. In short-term administration, tramadol i.v. has proven to have a higher association with nausea and vomiting than the oral application form [18, 35]. Of the oral preparations, the controlled-release ones seem to be more favorable regarding adverse effects such as nausea and vomiting [35]. It is well known that the use of total intravenous anesthesia is favorable regarding postoperative nausea and vomiting. Probably attributable to the gender of the study population (only women) [10, 18], the type of surgery and the preemptive application [36], the rate of nausea and vomiting was relatively high in both groups, but similar to those found in other studies [35, 37].

The overall low VAS scores indicate excellent results of general pain management in both groups, while the concept of preemptive analgesia might also have contributed to the low VAS scores [38, 39].

Our dosing scheme of 200 mg controlled-release tramadol twice in 24 h proved to be sufficient, while a placebo-controlled study analyzing the efficacy of controlled-release tramadol 100 mg in the management of postoperative pain after breast surgery found no effect on pain scores and morphine consumption combined with a higher rate of adverse events [40]. A maximum of 400–600 mg tramadol in 24 h is presently recommended by the German interdisciplinary expert committee for the treatment of perioperative and postoperative pain [41].

The possible doses of controlled-release oxycodone are not as limited as those recommended for tramadol [42, 43]. It therefore seems to be more advantageous to choose oxycodone to treat severe postoperative pain.

In summary, our results show that controlled-release oxycodone 20 mg and controlled-release tramadol 200 mg on a 24-hour dosing regimen are clinically equivalent with a similar side effect profile for postoperative analgesia in patients after surgery for breast cancer.

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